troglitazone

Company	**Sankyo Co Ltd**
Highest Dev Status	Withdrawn
Indications	Non-insulin dependent diabetes Diabetes mellitus
Actions	Insulin sensitizer PPAR agonist Hypoglycemic agent 5-HETE modulator

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Reason for update on 09 June 2004

1 reference added **[542814]**

Summary

Troglitazone, a peroxisome proliferator activated receptor (PPAR) agonist, was launched by Sankyo in Japan in April 1997, and in the US by Parke-Davis in March 1997 **[270683]** for the treatment of non-insulin dependent diabetes (NIDDM) **[237320]** but has since been withdrawn from these markets. Some preclinical data, reported in April 2000, described **troglitazone** as having potential as an anticancer agent in head and neck squamous cell carcinoma **[362460]**.

In March 2000, Warner-Lambert voluntarily discontinued the sale of **troglitazone** from the US market. The company decided, following discussions with the FDA, that it was in the best interests of patients to discontinue marketing **troglitazone** at that time **[360409]**. **The FDA** subsequently opened an investigation into allegations that Warner-Lambert had manipulated adverse-event reports regarding the toxic liver effects of **troglitazone** **[360696]**. Sankyo also voluntarily discontinued the sale of **troglitazone** in both Japan and the US **[363389]**. By January 2003, the FDA had withdrawn its approval **[476981]**.

In April 2000, class action lawsuits against Warner-Lambert and Parke-Davis were filed in the US District Court for the District of New Jersey and in the federal court in Philadelphia. The suits allege that the defendants misled potential users of **troglitazone** concerning the health risks associated with the drug and alleges that the defendant's product warnings were wholly inadequate and failed to warn prescribing physicians and patients of the actual heart and liver risks associated with the compound **[362272]**,

pioglitazone

Company	**Takeda Pharmaceutical Co Ltd**
Highest Dev Status	Launched
Indications	Hyperlipidemia Hypertension Myocardial infarction Atherosclerosis Cerebrovascular ischemia Non-insulin dependent diabetes
Actions	Insulin sensitizer PPAR gamma agonist Hypoglycemic agent Antihypercholesterolemic agent
Technologies	Tablet formulation

Related information
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Reason for update on 23 February 2006

Minor editorial amendment

Summary

Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, which, by late 2000, had been launched extensively by **Takeda** for the treatment of non-insulin dependent diabetes mellitus (NIDDM; type 2 diabetes) **[181756]**. Takeda was initially copromoting the drug in the US with **Eli Lilly**, and this was expanded to include more than 70 countries within Europe, the Middle East, Africa and Asia Pacific in August 1999 **[338000]**. The company is also developing the drug for the potential treatment of atherosclerosis, hypertension and for the potential prevention of myocardial infarction and stroke. In May 2003, it was in phase III trials for atherosclerosis **[491975]**; these trials were ongoing in March 2005 **[606970]**, **[515419]**. In November 2004, clinical data showing the efficacy of the drug for the treatment of hypertension were published **[570792]**, **[570772]**.

ATHEROSCLEROSIS

In November 2004, clinical data demonstrating the relative efficacy of pioglitazone (30 mg/day) compared to **rosiglitazone** (4 mg/day) on blood lipids and insulin sensitivity were presented at the AHA meeting in New Orleans, LA. Results from the randomized, double-blind, multicenter trial in 735 patients with type 2 diabetes showed that both drugs exhibited similar degrees of glycemic control. However, at week 24,

rosiglitazone

Company	**SmithKline Beecham plc**
Highest Dev Status	Launched
Indications	Alzheimers disease Psoriasis Rheumatoid arthritis Asthma Ulcerative colitis Non-insulin dependent diabetes
Actions	Insulin sensitizer PPAR gamma agonist Anti-inflammatory
Technologies	Tablet formulation

Related Information
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Reason for update on 09 February 2006

Minor editorial amendment, 1 reference added [**649382**]

Summary

Rosiglitazone (Avandia), a peroxisome proliferator-activated receptor (PPAR)-gamma receptor agonist, has been developed and launched in several major markets by **SmithKline Beecham** (SB; now GlaxoSmithKline, GSK) as a treatment for non-insulin dependent diabetes mellitus (NIDDM/type II) [**263572**]. It is also in development for several other indications, including Alzheimer's disease (AD) and asthma [**515870**], [**632116**]. It was launched in the US and Mexico for diabetes in June 1999 [**327686**], [**333230**], and by June 2000, had also been launched in the UK and Germany [**376124**]. By December 2003, the compound was in phase II trials for Alzheimer's disease (AD) [**515870**] and in November 2005 trials were ongoing [**638027**]; by February 2006, the company expected an extended-release formulation to enter phase II trials in Alzheimer's disease later that year [**649382**]. In July 2005, a phase II trial was initiated in asthma patients, due to be completed by March 2008 [**632116**]. In November 2005, phase II trials had been initiated in rheumatoid arthritis (RA) [**638027**]. By February 2006, Glaxo expected phase III trials of rosiglitazone with **simvastatin** (qv) to begin later that year [**649382**].

The compound has also previously been developed for psoriasis; in 2003, phase III trials for psoriasis were initiated [**515870**]. However, the results reported in October 2004 showed that the compound had no efficacy for this indication [**628420**], [**628419**] and no further development for psoriasis has been reported

The Investigational Drugs database

DRUG report

Drug Report

netoglitazone

Company	**Mitsubishi-Tokyo Pharmaceuticals Inc**
Highest Dev Status	Phase 2 Clinical
Indications	Metabolic disorder Non-insulin dependent diabetes
Actions	Insulin sensitizer PPAR gamma agonist PPAR alpha agonist PPAR delta agonist Hypoglycemic agent

Reason for update on 12 January 2006

Minor editorial amendment

Related Information

COMPANY

REFERENCES

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Summary

Perlegen and **Mitsubishi Pharma** (formerly Mitsubishi-Tokyo) are developing netoglitazone (MCC-555; RWJ-241947; isaglitazone), a thiazolidinedione triple peroxisome proliferation activated receptor (PPAR) agonist (alpha, gamma and delta), as a potential treatment for type 2 diabetes and other metabolic diseases **[204644]**, **[423717]**, **[594833]**. By March 2004, phase II trials had been initiated in Japan **[538366]**, **[520195]**; these trials were ongoing in November 2004 **[595948]**. In April 2005, Perlegen was planning US clinical trials **[594833]**.

Johnson & Johnson (J&J) was previously developing the compound outside of Japan and, in April 1999, had listed netoglitazone as being in phase II trials **[304271]**, **[322655]**; however, by May 2003, the agreement between Mitsubishi and J&J had been terminated **[491163]**.

PRECLINICAL DATA

In June 2003, preclinical data on netoglitazone were presented at the 63rd ADA meeting in New Orleans, LA. Netoglitazone inhibited TNFalpha-induced vascular cell adhesion molecule-1 (VCAM-1) expression in a dose-dependent manner in vitro. Monocyte chemotactic protein-1 (MCP-1) secretion from human aortic endothelial cells was dose-dependently inhibited by netoglitazone, suggesting beneficial effects on endothelium in early stage of atherosclerosis, mediated by PPAR alpha or PPAR delta **[492285]**.

The Investigational Drugs database

DRUG report

Drug Report

reglitazar

Company	**Japan Tobacco Inc**
Highest Dev Status	No Development Reported
Indications	Non-insulin dependent diabetes
Actions	Insulin sensitizer PPAR gamma agonist PPAR alpha agonist

Reason for update on 24 March 2004

5 references added [**515261, 389917, 431904, 473077, 464687**], indexing updated, literature evaluation added, one or more development status entries have been updated

Summary

Japan Tobacco was developing **reglitazar** (JTT-501), an insulin sensitizer and PPARalpha and gamma agonist, as a potential oral treatment for Type II diabetes [**249397**]. By 1998, **reglitazar** was in phase II trials in the UK for Type II diabetes [**290700**]; in July 2001, phase III trials were expected to commence later that year [**402336**]. However, in October 2002, the company decided to terminate development of the drug candidate based on an assessment of its results [**466412**].

Pharmacia Corp (formerly **Pharmacia & Upjohn**) had development and marketing rights worldwide except for Japan and Korea [**289901**], although in April 2002, the company reported that it was no longer involved in the development of **reglitazar** [**445305**]. Phase II trials had commenced in Japan, where Welfide (now Mitsubishi Pharma) was codeveloping the compound [**304419**]; however, there has been no development reported on this collaboration since 1998.

In September 2001, preclinical data were presented at the European Association for the Study of Diabetes meeting, Glasgow, UK. In vitro and in vivo studies suggested that **reglitazar** exerted its antidiabetic action, following a pathway similar to that through which insulin exerts its own effect [**429965**].

In June 2001, data on **reglitazar** were presented at the 61st ADA meeting in Philadelphia, PA. These data demonstrated that, in the Type II db/db male mice model, EC50 values (microM) for PPARalpha and gamma agonism were (alpha/gamma): **rosiglitazone** (qv) 0.1/5; **pioglitazone** (qv) 1/7; NNC-61-0029 (qv) 0.6/3; **reglitazar** 0.4/2; MCC-555 (qv) 3/0.1; **KRP-297** (qv) 0.5/0.4; GI-262570 (qv) 0.002/0.3; and, fenoacid

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Drug Report

farglitazar

Company	**Glaxo Wellcome plc**
Highest Dev Status	Phase 2 Clinical
Indications	Unidentified Fibrosis Cardiovascular disease Non-insulin dependent diabetes
Actions	Insulin sensitizer PPAR gamma agonist Retinoid X receptor modulator

Related information
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Reason for update on 02 December 2005

one or more development status entries have been updated, indexing updated

Summary

GlaxoSmithKline (formerly Glaxo Wellcome) is developing farglitazar (GW-262570) , a peroxisome proliferator-activated receptor (PPAR)-gamma agonist and retinoid x receptor modulator, for the potential treatment of hepatic fibrosis [**638027**], and investigating it for the potential treatment of cardiovascular diseases [**470611**], [**464521**]. In November 2005, farglitazar was in phase II trials for hepatic fibrosis [**638027**].

The compound was previously under development for type II diabetes, for which it reached phase III trials [**230289**], [**335170**], [**399771**], [**409231**]. However, in October 2001, it was reported that development of the compound for this indication had ceased as it did not meet its target profile. Alternative indications for the compound were being explored at that time, but the company would not disclose these, only revealing that the field would not be obvious to people who had not studied the group of compounds very closely [**426569**], [**427414**].

CARDIOVASCULAR DISEASE

In November 2002, preclinical data on farglitazar were presented at the AHA meeting in Chicago, IL. Rats receiving 8 mg/kg bid po farglitazar showed PPAR-gamma activation through detection of increased mRNA levels of the target genes FABP3 and aP2. Increased vasodilator NO levels ($p < 0.05$) and fluid retention were observed, while the glomerular filtration rate, effective renal plasma flow and renal filtration fraction

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Drug Report

YM-440

Company	**Astellas Pharma Europe BV**
Highest Dev Status	No Development Reported
Indications	Non-insulin dependent diabetes
Actions	Insulin sensitizer Hypoglycemic agent

Related Information

COMPANY

REFERENCES

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Actions

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Reason for update on 24 March 2004

1 reference added [**390055**], indexing updated, one or more development status entries have been updated, indexing updated, one or more development status entries have been updated

Summary

Yamanouchi Europe was developing **YM-440**, an insulin sensitizer, for the potential treatment for non insulin-dependent diabetes. The company had begun phase II trials in Europe by 1999 [**326891**]; however, the compound has not appeared on a company pipeline since May 2000 [**365756**], and no further development has been reported since. By May 2002, **YM-178** (qv), a beta 3 receptor agonist, appeared to have superceded **YM-440** in Europe for this indication.

An oral dose of **YM-440** 30 mg/kg od, for four days caused a reduction of 39% in blood glucose levels in male mice. Although similar in some respects to **troglitazone** (qv), Yamanouchi claims that **YM-440** has a different mechanism of action to the thiazolidinediones as a class. Specifically, **YM-440** showed only weak activity against PPAR-gamma [**279360**].

Administration of 100 mg/kg, **YM-440** to diabetic db/db mice for two weeks significantly decreased blood glucose concentrations (418 to 243 mg/dl); notably, there was no significant increase in body weight gain at the end of the treatment (in contrast to **troglitazone** and **pioglitazone**, (qv)). **YM-440** did not affect PPAR-gamma activity [**293702**].

YM-440 is (Z)-1,4-bis-4-[(3,5-dioxo-1,2,4-oxadiazolidin-2-yl-methyl)]phenoxybut-2-ene [**293702**].

In February 1999, Lehman Brothers predicted the first major product launch to be in 2002, with sales

KRP-297

Company	**Kyorin Pharmaceutical Co Ltd**
Highest Dev Status	Discontinued
Indications	Hyperlipidemia Non-insulin dependent diabetes
Actions	Insulin sensitizer PPAR gamma agonist PPAR alpha agonist Antihyperlipidemic agent
Technologies	Tablet formulation

Related information
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Reason for update on 30 August 2005

1 reference added [**620284**]

Summary

Merck & Co subsidiary Banyu, in collaboration with Kyorin, was developing **KRP-297** (MK-767, L-410198), a PPAR alpha and gamma agonist, for the potential treatment of diabetes and hyperlipidemia [**311944**], [**506609**]. By September 2002, the companies were conducting phase II trials in Japan [**488534**], [**516815**]. Merck had initiated phase III trials in December 2002 [**473816**], but discontinued development in November 2003 for safety reasons [**514245**]. In December 2003, Kyorin announced that it was also discontinuing the development of **KRP-297** [**520055**].

As of December 2002, Merck had been developing **KRP-297** as MK-767 [**473816**]; however, in November 2003, the company discontinued its phase III development program because a long-term safety assessment program had identified a rare form of malignant tumors in mice [**514245**]. At this time, Kyorin was in discussion with Merck on the future development of **KRP-297** in Japan [**518196**].

CLINICAL STUDIES

In March 2003, clinical data on **KRP-297** were presented at the Lorenzini Foundation's Second International Meeting on PPARs in Florence, Italy. A double-blind, randomized, placebo-controlled, single-dose trial was performed to determine the safety, tolerability, pharmacokinetics and lipid effects of **KRP-297**. Single oral doses from 1 to 80 mg were well tolerated. Plasma AUC and Cmax values increased with dose and the terminal half-life of **KRP-297** was 36 h. A standard breakfast did not affect the absorption of a 5 mg oral

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LY-282449

Company	**Eli Lilly & Co**
Highest Dev Status	No Development Reported
Indications	Diabetic complication
Actions	Insulin sensitizer PPAR gamma agonist

Reason for update on 05 November 2002

Indexing updated

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Summary

TA-174 is a thiazolinedione peroxisome proliferator-activated receptor (PPAR) gamma agonist which was under investigation by Eli Lilly in collaboration with Tanabe as a hypoglycemic agent for the potential treatment of diabetic complications. Lilly discontinued development of the drug in 1993 due to toxicity problems [**155124**] and although Tanabe continued to investigate the compound, no development has been reported by the company since 1997 [**367139**].

Development Status

HISTORY

Detailed status for **Eli Lilly & Co**

Indication	Country	Status	Reference	Date
Diabetic complication	US	Discontinued	**155124**	01 September 1993

Detailed status for **Tanabe Seiyaku Co Ltd**

Indication	Country	Status	Reference	Date
Diabetic complication	Japan	No Development Reported		18 May 2000

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NC-2100

Company	**Nippon Chemiphar Co Ltd**
Highest Dev Status	Discovery
Indications	Non-insulin dependent diabetes
Actions	Insulin sensitizer PPAR gamma agonist

Reason for update on 08 May 2003

1 reference added [**488447**]

Related information

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Summary

NC-2100 is a thiazolidinedione PPAR-gamma activator which is under investigation by Nippon Chemiphar for the potential treatment of diabetes. In KKAy obese mice **NC-2100**, 0.1% for two weeks, lowered plasma glucose and triglyceride concentrations to levels comparable to those achieved with PPAR-gamma activators such as **pioglitazone** (qv) and **troglitazone** (qv) [**371071**].

Development Status

Detailed status for **Nippon Chemiphar Co Ltd**

Indication	Country	Status	Reference	Date
Non-insulin dependent diabetes	Japan	Discovery	**371071**	16 June 2000

Chemistry

Structure

VIEW MOLFILE

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DRUG report

Drug Report

muraglitazar

Company	**Bristol-Myers Squibb Co**
Highest Dev Status	Pre-registration
Indications	Metabolic disorder Non-insulin dependent diabetes
Actions	Insulin sensitizer PPAR gamma agonist PPAR alpha agonist Hypoglycemic agent Antihyperlipidemic agent
Technologies	Oral formulation

Related information
COMPANY
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Reason for update on 22 December 2005

one or more development status entries have been updated, 1 reference added **[642539]**

Summary

Bristol-Myers Squibb (BMS) is developing muraglitazar (BMS-298585; Pargluva; structure shown), a dual PPAR alpha/gamma agonist, as a potential oral treatment for type 2 diabetes and other metabolic disorders. An NDA was submitted in December 2004 **[577532]**. In October 2005, the FDA issued an approvable letter requesting additional information to support the cardiovascular safety profile of the drug **[629049]**. Later that month, BMS announced its would have to complete additional trials to secure approval. These were expected to take 5 years. At that time, BMS intended to meet with the FDA to discuss its options, including discontinuing development **[630997]**. By December 2005, discussions with the FDA were ongoing **[642539]**.

Merck & Co was codeveloping the drug with BMS. However on receipt of the FDA approvable letter in October 2005, the companies began discussions to terminate the collaboration **[630997]**. In December 2005, BMS and Merck reached an agreement for the return of the drug to BMS **[642539]**.

By March 2003, **backup compounds** (qv) were also under investigation **[486672]**.

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tesaglitazar

Company	**AstraZeneca plc**
Highest Dev Status	Phase 3 Clinical
Indications	Heart arrhythmia Lipid metabolism disorder Insulin dependent diabetes Non-insulin dependent diabetes
Actions	PPAR gamma agonist PPAR alpha agonist Hypoglycemic agent Antiarrhythmic agent Antihyperlipidemic agent
Technologies	Oral formulation

Related information

COMPANY

REFERENCES

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Reason for update on 10 February 2006

1 reference added [**648528**], Minor editorial amendment

Summary

AstraZeneca (formerly **Astra**) is developing tesaglitazar (AZ-242, AR-H039242, Galida; structure shown), an oral dual PPAR alpha/gamma agonist, for the potential improvement of dyslipidemia and glycemic control in type 2 diabetics [**275466**], [**377656**]. In October 2003, phase III trials were being initiated [**507400**], [**507401**]; these were ongoing in October 2004. At that time, the anticipated filing date was moved from 2006 to 2007 as a result of AstraZeneca agreeing to extend long-term follow-up studies to 2 years following a worldwide regulatory authority review of the safety and toxicology of PPAR agonists [**563036**]. In November 2005, phase II trials were underway in Japan [**638194**]. By September 2005, tesaglitazar was on track for a 2007 submission [**624516**]; in February 2006, the expected submission date of the second half of 2007 was dependent upon the results of ongoing phase III studies and discussions with the FDA [**648480**], [**648528**].

In December 1999, the compound was also being developed as a potential antiarrhythmic drug [**349551**], [**314472**], [**377656**]; as of March 2001, however, diabetes and insulin resistance were the only indications listed on the company's pipeline [**402040**].

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ragaglitazar

Company	**Dr Reddys Research Foundation**
Highest Dev Status	Discontinued
Indications	Hyperlipidemia Non-insulin dependent diabetes
Actions	Insulin sensitizer PPAR gamma agonist PPAR alpha agonist Hypoglycemic agent Antihyperlipidemic agent

Related information
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Reason for update on 05 May 2004

Minor editorial amendment, one or more development status entries have been updated, literature evaluation added, indexing updated

Summary

Ragaglitazar (NN-622, (-)DRF-2725; structure shown), a PPAR (peroxisome proliferator-activated receptor) alpha and gamma agonist that regulates blood glucose and lipid levels, was being developed by **Novo Nordisk** (previously in collaboration with **Novartis**), under license from Dr Reddy, for the potential treatment of non-insulin dependent (Type II) diabetes **[325344]**, **[416231]**. In November 2001, phase III trials were initiated both in the US and in Europe **[428278]**, **[440091]**. In February 2002, these phase III trials were ongoing but **Novo Nordisk** revealed that it was planning to outlicense the compound **[443186]**, **[438928]**. In July 2002, **Novo Nordisk** decided to suspend all current clinical trials of **ragaglitazar** and postponed all planned future trials. This decision was made in response to preclinical studies that revealed the formation of bladder tumors in one mouse and a number of rats after treatment with the drug. At this time, the company planned to continue all other activities in the development program until it completed a renewed benefit/risk assessment of **ragaglitazar**, the results of which would be ready by the first quarter of 2003. Filing for approval was expected to be delayed by two years **[458773]**, **[458774]**, **[460379]**. However, by February 2003, **Novo Nordisk** had decided not to pursue further development of the program **[478217]**, **[478168]**.

CLINICAL INFORMATION

Worldwide phase II trials had begun by September 2000 **[381826]**, **[385666]**. By July 2001, **Novo Nordisk** expected to complete phase II trials later in that year **[416231]**; and, by September 2001, the